Pharmacokinetic Modeling of ETS Exposure

Motivation

"OSHA would like to consider the use of a PBPK model in an effort to develop a clear and complete picture of factors that may affect:

- environmental exposure measurements,
- internal dose estaimates, and ultimately
- estimates of expected risks

attributed to ETS exposure at the workplace."

"OSHA is seeking comment on appropriate methodology, available data etc."

Risk Assessment Requires

determination of extent of exposure

- airborne chemicals, particulate concentrations
- **internal** measure of individual exposure (**biomarker**)

Selection of Biomarker

relevance to specific end points

- cardiovascular disease
- lung cancer

Cardiovaskular Effects of ETS

associated with

- CO
- nicotine
- PAHs

Compound	Possible Biomarker	Specific for ETS	Biokinetic Information Available
CO	HbCO (blood)	no	yes
nicotine	nicotine, cotinine (body fluids)	(yes)	yes
PAHs (particles	- solanesol	no yes	- no)

Conclusion: to relay on **nicotine/cotinine** as a specific and relevant biomarker for ETS exposure

Lung Cancer

- "...mechanisms of carcinogenicity from exposure to ETS is not known."
- "...most of identified carcinogens of ETS are not unique to ETS."

⇒ impossible to identify specific compounds as biomonitor

best choice: biomarker which provides the most general representation of all components of ETS

⇒ **nicotine** (unique, GVP and PP)

- strong correlation between nicotine in air and mutagenicity of ETS (equal or better relationship than RSP)
- positive correlation between short-term mutagenicity tests and carcinogenicity

conclusion: "...the use of **nicotine** as an exposure marker for carcinogenic effects of ETS appears to be justified."

Cotinine as Biomarker for ETS

strong correlation between

- nicotine intake and plasma cotinine levels
- cotinine in body fluids and ETS exposure
- cotinine in saliva and cotinine in plasma
- cotinine in plasma and urinary excretion of cotinine

assumption: Kinetics parameter for nicotine and cotinine can be extrapolated from smokers to nonsmokers.

Esp. Studies on children data!

difficulties

- nicotine in diet
- possibility of longer half-life of cotinine at very low concentrations (slow release of nicotine from binding sites)

⇒ OSHA seeks comment and data on these issues.

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